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Friday, September 08, 2000

Dockets Management Branch (HFA-305) Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

Re: Draft revised guidance entitled "Q3B(R) Impurities in New Drug Products." Fed. Reg. Vol. 65 No. 139, July 19, 2000

Sir/Madam:

On behalf of the International Association of Innovative and Generic Manufacturers (IAGIM), I am submitting comments and objections on "Impurities in New Drug Products" Docket No. 96D 0009, FR. Vol. 65 No. 139, July 19, 2000.

IAGIM is comprised of manufacturers and developers of generic and innovative drugs worldwide as well as the providers of technical services and drug development know-how to these firms and institutions. Many of our members will be directly impacted by implementation of the rounding-up paragraph in the proposed guideline, amending the agency's current regulations on "Impurities in New Drug Products" with specific respect to the cost and identification parameters impacting on the eventual approved application.

IAGIM has long taken a leading role in advocating for harmonization of laws and regulations through its official publication The Int. J. of Generic Drugs, that assures the most expeditious availability of high-quality, low-cost generic and innovative drug development and end products to global drug consumers, not solely limited to the US and EU.

As these guidelines impact on the drug development costs, the cost of establishing an overall drug product impurity profile, at all FDA approved global drug development sites (whether in the US, EU or ROW) will be significantly increased with no significant clinical or adverse effects benefit.

No logical scientific benefit or mathematical logic based on good scientific practice has been demonstrated by such a rounding definition which will impact negatively on the cost of developing the drug product impurity profile as currently used in the drug development and generic know-how technology development units in the US, EU and Rest of the World where these drug development establishments are required to meet either the US and/or EU guidelines for harmonization, marketing or other purposes. Thus, we are pleased to offer the following comments on the proposed regulations with respect to matters of rounding procedures.

OVERVIEW

While IAGIM recognizes the initial work and joint intellectual effort input by the US and EU agencies (via ICH) in developing these New Drug Products impurity proposals, IAGIM is concerned that several elements of the proposal, place more significance on rounding-up and rounding-down procedures to the number 0.1% of the labeled amount (which represents the level at where impurity/degradant identification is generally required) than on the proper scientific interpretation of rounding impurity levels to the most significant figures as appropriate to the quantitation limit (QL) of the (said) HPLC or other instrument test method.

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As modern HPLC methodology can readily and routinely detect individual impurities to the second and third decimal places (namely 0.046% of labeled amount) and can accurately distinguish a difference between 0.050 and 0.075; It violates good scientific rounding procedures to regard these two accurate accessed impurity values, by agency regulation, as both equal to 0.1% by imposing an arbitrary rounding definition and then limiting the end value to only one decimal place.

In the best case scenario, the limit of impurities and degradants should be limited to two significant decimal places with reference to the pivotal value of 0.1%, which is the recognized cut-off identification value and has attached to it an existing agency guideline definition requiring further development and identification (with the incorporated increased development and assay costs).

For this reason, and other specific reasons mentioned herein, TAGIM opposes the proposed definition and example of rounding as found in the proposed revised glossary namely;

Proposed Definition

Rounding: The process of reducing a result to the number of significant figures or number of decimal places as dictated by the appropriate limit. For example, a result greater than or equal to (\geq) 0.05 and less than ($<$) 0.15 is rounded to 0.1.

IAGIM offers the following definition to the glossary to clarify the regulations and improve the procedural practice of rounding up or down.

Amended Definition

Rounding: The process of rounding a result to the number of significant figures or a number of appropriate decimal places. For example, a percentage result in the range of 0.055 - 0.064 shall be rounded-up to 0.06 and a percentage result, in the range of 0.146 - 0.154 is rounded to 0.15...

Furthermore appropriate sections of the guideline text should be amended to meet all numerical situations where rounding may occur so as to standardize any impurity assay results so obtained to TWO significant decimals where the values have exceeded the Quantitation Limit (QL) capability for the assay of the instrument being used.

It must be clearly stated that good science dictates that rounding procedures are to be solely used for mathematical standardization and data clarity so that results can be simply understood by all concerned without compromising accuracy of individual results and furthermore it should not be used, as in the above rounding examples, to obtain an arbitrary percentage value. FDA's rounding procedures on the percentage of impurity assay values found between 0.050 to 0.095% are to be rounded as 0.1%, a value which has attached to it, an accepted agency guideline definition. (i.e. identifying the molecular impurity structure).

Currently impurity structures should be identified when their percentage of the labeled amount is 0.1% or greater. The current procedures do not call for impurity or degradant identification of the molecular structure that has a HPLC peak count equivalent to 0.05, 0.06% or for that matter 0.09% of the labeled amount.

Under the proposed definition, as stated in the glossary, future impurity structures (impurities and/or degradants) would be identified when their percentage of the labeled amount is 0.05% or greater, if the agencies arbitrary rounding-up definition were to be applied.

This procedure will in fact reduce by 50% the assay percentage level (Table 1) where impurities need to be identified and where their status change from 'unknown impurities' to 'known impurity structures'. Although this draft revised guidance represents the agency's current thinking on impurities in new drug products, it does not create or confer any rights for or on any person and does not operate to bind FDA or the public. However the down-the-line impact on new drug development and subsequently generic equivalents on patent expiry will eventually be open the same arbitrary rounding procedures which may by default become the future industry standard for both the innovative and generic drug industry, thus increasing the overall cost of drug quality control.

The agency has not demonstrated with any appropriate supporting scientific database evidence that there is a need to reduce the assay peak count for impurity/degradation identification from the currently 0.1% standard to a proposed 0.05%, as will be effected by the apparent arithmetic outcome of the proposed agency rounding procedure.

Furthermore the agency has not shown any toxicological evidence, whether of a general or specific nature, based on drug impurity profile percentages vs. patient clinical benefits to warrant that such a change is either reasonable, justifiable or in the public health interest.

TABLE I.

Impurity Percentage	Rounded to Significant Figures	FDA and EU New Proposal
0.050 - 0.054	0.050	0.10
0.055 - 0.059	0.060	0.10
0.060 - 0.064	0.060	0.10
0.065 - 0.069	0.070	0.10
0.070 - 0.074	0.070	0.10
0.075 - 0.079	0.080	0.10
0.080 - 0.084	0.080	0.10
0.085 - 0.089	0.090	0.10
0.090 - 0.094	0.090	0.10
0.095 - 0.099	0.10	0.10

Key:

SIGNIFICANCE	EXAMPLE
One Significant decimal place	0.1[x]
Two Significant decimal places	0.05[x]
Three Significant decimal places	0.095[x]

[x] = The value of this decimal imparts significance to the decimal on the immediate left of it. This is the mathematical meaning of SIGNIFICANCE. When this value is equal or greater than [x] = 5 only the decimal on the immediate left is rounded up, and the result is reported to one, two or three significant figures. Rounding can only occur once in a numerical set
Sincerely,

Jeremy. D. BLOCK
BSc, MPS, D. Pharm (Wits)
Senior Research Scientist.
IAGIM Scientific Review Committee.

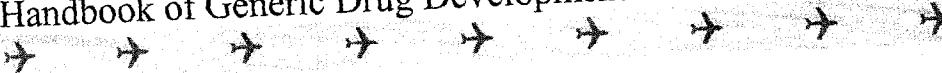
~~John Stark~~

06. Sept 2000



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